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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/044,359 | 01/11/2002 | Rafael Hermann | BB1367 US CNT | 9202 |

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E I DU PONT DE NEMOURS AND COMPANY
LEGAL PATENT RECORDS CENTER
BARLEY MILL PLAZA 25/1128
4417 LANCASTER PIKE
WILMINGTON, DE 19805

| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | 4 |

DATE MAILED: 03/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/044,359 | HERMANN ET AL. | |
| | Examiner | Art Unit | |
| | Jeanine A Goldberg | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *18-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0102* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This action is in response to the papers filed January 11, 2003. Currently, claims 18-31 are pending.

### *Drawings*

2. The drawings have been amended to include various domains which are supported by the specification. The drawings however are objected to because the added notations are illegible.

3. Upon comparison of SEQ ID NO: 2 presented in the figure and SEQ ID NO: 2 presented in the sequence listing, the sequences are different. SEQ ID NO: 2 in the sequence listing is 58 amino acids in length whereas the figure depicts 57 amino acids. It appears as though the final lysine (K) is missing from the figure. It is unclear which sequence is correct. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 18-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides which encode a polypeptide with cobatoxin activity which have a sequence identity of at least 80%, 85%, 90% and 95% to SEQ ID NO: 2. The claims encompass any sequence which minimally has 80% identity with SEQ ID NO: 2.

The specification fails to teach a single disclosed species within the scope of the claims. The specification teaches a nucleic acid encoding SEQ ID NO: 2.

The specification fails to provide any evidence that SEQ ID NO: 2 is infact a cobatoxin, aside from the 36.2% identify of the protein to known *Centruroides noxuis* cobatoxin 1.

There is not adequate description of the genus of cobatoxin polynucleotides which encode a polypeptide which have a sequence identity of at least 80%, 85%, 90% and 95% to SEQ ID NO: 2. The specification fails to discloses a single polynucleotide within the scope of the genus: polynucleotides which encode a cobatoxin polypeptide which have a sequence identity of at least 80% to SEQ ID NO: 2. The general knowledge in the art concerning polynucleotides which encode a cobatoxin polypeptide which have a sequence identity of at least 80% to SEQ ID NO: 2 does not provide any indication of how to readily identify these sequences.

SEQ ID NO: 2 has utility based upon the ability to reduce activity of larvae (pg 31).

Specifically, SEQ ID NO: 2 is 58 amino acids in length. The specification does not teach that this sequence is a cobatoxin. The claims encompass variants and homologs of SEQ ID NO: 2 such that there is substantial variability among the species

of nucleic acids encompassed in the broad scope of the claim. The specification has also not defined a structural feature of the nucleic acids which would be common to all members of the genus such that the artisan would be able to determine whether the claimed nucleic acid encodes a cobatoxin. While the specification teaches the conserved cysteine residues are probably involved in intrachain disulfide bridges, the specification does not teach any functional assay which identifies the polynucleotide as encoding a cobatoxin. Moreover, it is unclear what constitutes a cobatoxin therefore SEQ ID NO: 2 does not constitute a substantial portion of the genus.

While the specification and the art teach teach two specific cobatoxins, namely cobatoxin 1 and 2, there is no definition of what constitutes a cobatoxin activity. Furthermore, one of skill in the art would conclude that applicant was not in possession of the claimed "polynucleotides which encode a cobatoxin polypeptide which have a sequence identity of at least 80%, 85%, 90% and 95% to SEQ ID NO: 2" because the lack of description of what constitutes a single member of this genus is not representative of the variants of the genus and is insufficient to support the claims. Thus, the specification does not adequately provide a written description for polynucleotides which encode a cobatoxin polypeptide which have a sequence identity of at least 80%, 85%, 90% and 95% to SEQ ID NO: 2.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 18-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide which encodes a polypeptide having a 100% sequence identity with SEQ ID NO: 2, does not reasonably provide enablement for an isolated polynucleotide which encodes a cobatoxin polypeptide, the polypeptide having 80%, 85%, 90%, 95% or 100% sequence identity with SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to an isolated polynucleotide which encodes a cobatoxin polypeptide the polypeptide having a sequence identity of at least 80%, 85%, 90% and 95% to SEQ ID NO: 2.

The specification teaches scorpion venoms have been recognized as a source of peptidyl inhibitors of various types of potassium ion channels (pg 1). The specification teaches that potassium channel modifies are small polypeptides which form compact structures kept rigid by three disulfide bridges. The specification teaches that cobatoxin 1 and 2 are potassium channel blocking toxins isolated from scorpions and which have 32 amino acids and contain 3 disulfide bridges (pg 2, lines 28-32). The specification also teaches that leiuropeptides I, II and II are peptides with cysteine pattern analogous to that of short-chain scorpion toxins which act on potassium channels and have 31 amino acids and a positively charged region that binds to receptors. Leiurotoxin I is a 31 amino acid peptide with three disulfide bridges holding the amino-terminal alpha

structure on the side of the carboxy-terminal two beta barrels (pg 2, lines 33-37). Moreover, the specification teaches that SEQ ID NO: 2 shows 36.2% amino acid homology to scorpion cobatoxin 1. Figure 1 illustrates the six conserved cysteine residues probably involved in intrachain disulfide bridges (pg 5, lines 5-10). The specification asserts that the nucleic acids are K-channel modifiers based upon their homology to known K-channel modifiers. Additionally, the specification provides a study which compares activity of SEQ ID NO: 2 in a assay which studies activity of encoded peptides against *Heliothis Virescens*. As provided in Table 3, 4 5-day old larvae were fed 200 mg of viral-contaminated diet. The larvae were examined for symptoms such as low diet consumption and a retardation in growth as compared to wild-type AcNPV fed larvae and insects which were fed control diet such that all larvae survived. The specification fails to teach that SEQ ID NO: 2 is a cobatoxin.

The art teaches isolation of two short toxins from venom of the scorpion C. noxius Hoffmann, named cobatoxins. Selisko (Eur. J. Ciochem. Vol. 254, pages 468-479, 1998) teaches that their primary structures show similarity to scorpion K-toxins. Selisko states that based upon the comparison of cobatoxin to existing subfamilies, cobatoxin 1 and cobatonxin 2 do not present sequence identities high enough to be grouped into any of the subfamilies and thus are in a separate subfamily (page 472, col. 2). Selisko performed functional tests for the cobatoxins. Therefore, given the teachings in Figure 7, Selisko does not believe that sequence identity of less than 40% can allow for classification. Selisko also analyzes the percent identities within the subfamilies which range between 41.4and 97%. Selisko teaches that functional tests of

the cobatoxins were performed to identify the toxins as K-toxins by their ability to displace I-noxiustoxin from its binding site in rat brain synaptosomes. Selisko also teaches the toxins were tested on two voltage-dependent K channels.

While the specification teaches assignment of amino acids as a cobatoxin based upon sequence identity and a conserved region of cysteine residues, the art does not support prediction of a functional correlation with regard to the presence of these cysotine residues or sequence identity. SEQ ID NO :2 and Genbank Accession A59440 are 54.5% identical. Genbank A59440 is described as a neurotoxin BmK37. Additionally, the art teaches that neurotoxin BmP05 precursor is 38.3% identical to SEQ ID NO: 2 (Genbank Accession Number Q9TVX3). The art teaches that the SEQ ID NO: 2 protein is 34.7% identical to Leiuropeptide III DNA (Genbank Accession Number AAB60782). The art teaches that the androctonus australis potassium channel agonist kaliotoxin 2 precursor is 31.8% identical to SEQ ID NO: 2 (Genbank Accession Number AAY99584). Further, Herrmann et al (Genbank Accession Number AAY99584) teaches that the toxin contains three disulphide bonds. Moreover, yhe art teaches that scorpion leiuropeptide I protein from Hottentotta judaica is 31.4% identical to SEQ ID NO: 2 (Genbank Accession Number AAB60781).

As also seen in the alignment provided by Selisko, all of the K+-channel-blocking scorpion toxins contain cysteine amino acids which are conserved between all 9 of the subfamilies. The art appears to teach numerous proteins that are not cobatoxins which are very close in identity with the conserved cysteine amino acids structure.. Therefore,

the presence of conserved cysteine does not seem to provide a predictable correlation with regard to function between cobatoxins and other toxins.

Neither the specification nor the art provides enough guidance to use the invention as broadly as claimed. The specification provides a homology study of the protein to known *Centruroides noxuis* cobatoxin 1 with SEQ ID NO: 2 from *Hottentota judaica*. The comparison reveals a 36.2% identify between the two proteins. The art teaches several additional scorpin toxins which are 54.5%, 38.3%, 34.7%, 31.8% and 31.4% identical to SEQ ID NO: 2 which also have three apparent disulfide bridges. SEQ ID NO: 2 appears to be more than 36.2% identical with neurotoxin BmK37 (Genbank Accesion Number A59440- 54.5% idetntity) and neurotoxon BmP05 (Genbank Accession Number Q9TVX3- 38.3% identity). Therefore, based upon homology, there appears to be more closely homologous sequences aside from cobatoxins. Moreover, Selisko classifies BmP05 as a Scyllatoxin-type subfamily 5 member rather than a cobatoxin-type subfamily 9. Selisko specifically states that cobatoxin 1 and cobatoxin 2 do not present sequence identities high enough to be grouped into any of the previously existing subfamilies based upon homology studies. The homology of cobatoxin 1 and 2 shared less than 40% identity with other toxins. Selisko failed to place cobatoxin 1 and 2 into subfamilies, e.x. subfamily 2, 3, 5, which has higher than 36% identity based upon the low sequence identity. Additionally, each of the subfamilies share between 41.4% and 97.1% identity. Subfamilies do not share less than the 41.4% identity. Thus, given the teachings here that SEQ ID NO: 1 shows

only 36% identity with cobatoxin 1, it is unlikely that Selisko would find that the sequence identity alone is high enough to be grouped into the subfamily of cobatoxins.

Moreover, the specification provides no functional assay to determine which proteins are cobatoxins. The specification nor the art has provided the apparent residues or domains which are fundamental to the properties of the cobatoxin such that the skilled artisan may recognize which positions within the amino acid and nucleic acid may be altered. The skilled artisan would first have to develop an assay to measure cobatoxin activity. Then the skilled artisan would be required to test and determine whether the nucleic acids which were not 100% identical to SEQ ID NO: 2 had the same functional properties as SEQ ID NO: 2. Absent factual evidence, a percentage sequence similarity of less than 100% to the entire sequence is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecules of 80% identity and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Assignment of a nucleic acid encoding SEQ ID NO: 2 as a cobatoxin is unpredictable. The protein has 36.2% identity to cobatoxin 1, however the protein also has comparable identity to

proteins which are *not* cobatoxins. Further, a nucleic acid encoding SEQ ID NO: 2 which has 80% identity and is a cobatoxin requires undue experimentation for the skilled artisan to make or use the claimed invention as broadly as claimed. The skilled artisan would be required to test each nucleic acid permutation which has 80% identity to determine whether the nucleic acid is a cobatoxin using an undisclosed assay for determining the assignment of a nucleic acid as a cobatoxin.

### *Allowable Subject Matter*

6. The nucleic acid encoding a polypeptide of SEQ ID NO: 2 appears to be novel over the prior art. Figure 3, page 31-32, illustrates SEQ ID NO: 2 (clone ibj1c.pk007.k8) was slightly active on *Heliothis virescens* larvae in two experiments. The specification defines "slightly active" as the larvae which had low diet consumption and a retardation in growth.

### *Conclusion*

**7. No claims allowable.**

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
March 26, 2003

**JEHANNE SOUAYA**
**PATENT EXAMINER**

Jehanne Souaya
3/27/03